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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
| 10/573,162 | 05/05/2006 | Fabrizio Gasparini | 33364-US-PCT | 6619 |
| 67283 | 7590 | 05/14/2010 | EXAMINER | |
| MONTGOMERY, MCCRACKEN, WALKER & RHOADS, LLP | | | ROBINSON, BINTA M | |
| 123 SOUTH BROAD STREET | | | ART UNIT | PAPER NUMBER |
| AVENUE OF THE ARTS | | | | 1625 |
| PHILADELPHIA, PA 19109 | | | | |
| MAIL DATE | | DELIVERY MODE | | |
| 05/14/2010 | | PAPER | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | |
|------------------------------|--------------------------------------|---|
| Office Action Summary | Application No. 10/573,162 | Applicant(s) GASPARINI ET AL. |
| | Examiner BINTA M. ROBINSON | Art Unit 1625 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on Applicant remarks filed 1/25/2010.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1 and 3-6 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1 and 4-6 is/are rejected.
- 7) Claim(s) 3 is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO/SB/06)
 Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____
- 5) Notice of Informal Patent Application
 6) Other: _____

1. (Detailed Action)

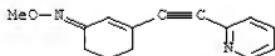
2. Modified rejection

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1, 4, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hcaplus Abstract 2001:167983 (WO 200101621, Cosford et. al.), and further in view of Blake et. al. and Patani et. al.

Hcaplus Abstract 2001:167983 teaches the compound



. The difference between the prior art compound and the instantly claimed compounds and compositions is the teaching of a substitution at the 2 position of the pyridyl ring in the instant claims which is methyl, versus the lack of substitution and the presence of a hydrogen atom at the 2-position in the prior art and the other difference is R moiety which is a radiolabeled methyl (radiolabeled with stable isotopes) in the instant compound versus can an unradiolabeled methyl in the prior art. The instant compounds are bioisosteres of the prior art compounds. Patani teaches that bioisosteres are compounds that elicit similar biological activity which is attributable to common physicochemical properties. See page 3148 of Patani et. al. Patani also teaches that Langmuir compared the physical properties of various molecules and

found them to be similar, and identified 21 groups of isosteres. Patani et. al. teaches that the widespread application of the concept of isosterism to modify biological activity has given rise to the term bioisosterism, and that more recently, the definition of bioisosterism has been broadened to mean "compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties..." See page 3148. Patani et. al. also teaches that the critical component of bioisosterism is that bioisosteres affect the same pharmacological target as agonists or antagonists and thereby, have biological properties which are related to each other. Page 3152 of Patani et. al. teaches that methyl is a bioisosteric replacement for hydrogen.

Blake et. al. teaches that Stable isotopes are proving useful as tracers for drug distribution and metabolism studies. See page 385 of Blake et. al. Blake also teaches that the many advantages of stable isotopes for these purposes include the absence of possible radiation hazards, especially important where children and pregnant women are concerned.

The instant compounds are radiolabeled bioisosteres of the prior art compounds. Cosford et. al. (See WO 2001016121) teaches that the prior art compounds can modulate metabotropic glutamate receptors. See page 120, claim 61 of Cosford.

It would have been obvious to one of ordinary skill in the art to synthesize radiolabeled bioisosteres of this class of compounds for use as neuroimagers since radiolabeled compounds radiolabeled with stable isotopes are useful as tracers for drug distribution and metabolism studies. It would have been obvious for one of ordinary skill

in the art to modify the prior art compounds to synthesize bioisosteres of the prior art compounds, because the field of neuroimaging includes the use of various techniques to either directly or indirectly image the structure, function/pharmacology of the brain. It is a relatively new discipline within medicine and neuroscience/psychology.

Neuroimaging falls into two broad categories:

- Structural imaging, which deals with the structure of the brain and the diagnosis of gross (large scale) intracranial disease (such as tumor), and injury, and
- Functional imaging which is used to diagnose metabolic diseases and lesions on a finer scale (such as Alzheimer's disease) and also for neurological and cognitive psychology research and building brain-computer interfaces.

Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds and compositions over those of the prior art compounds.

Claim 3 is objected to for being based on a rejected claim.

Response to applicant's remarks

The applicant traverses the above rejection alleging that under all of the definitions for bioisosteres in Patani et. al., that methyl is not a bioisosteric replacement for hydrogen. However, Patani et. al. at page 3148, says that the critical component of bioisosterism is that bioisosteres affect the same pharmacological target as agonists or antagonists and thereby, have biological properties that are related to each other. The prior art

compound affects the same pharmacological target as the instant compound, which is the metabotropic glutamate receptor, and therefore, under this definition of bioisosteres in Patani et. al., the prior art compound and instant compound have properties that are related to each other in view of Patani et. al. Page 3147 of Patani et. al., also states that bioisosterism represents one approach used by the medicinal chemist to modify compounds in more clinically effective agents. At page 3153 of Patani et. al., Table 2, it is demonstrated that the bioisostere replacements of methyl for hydrogen under Grimm's Hydride displacement law, were more potent than the unsubstituted compound (compound 20e) bearing only hydrogen. Table 2, demonstrates that the methyl analogue for Benzo [f]quinazolin-1 (2H)-ones were more clinically effective. Table 2 at page 3148, shows that fluorine, hydroxyl, NH₂, and methyl are bioisosteres of one another. Page 3149, also states that fluorine and hydrogen are bioisosteric replacements of one another. Subsequently, if fluorine, hydroxyl, NH₂, and methyl are bioisosteres of one another and flourine and hydrogen are bioisosteres of one another, one of ordinary skill in the art would be led to conclude that methyl and hydrogen are bioisosteres of one another, also in view of the fact that Patani et. al, states that methyl is a bioisosteric replacement for hydrogen at page 3152. In view of the fact, that the prior art compound and instant compound have the same pharmacological target – that of the mGlu receptor, and that Patani et. al., has shown that methyl analogues of compounds (unsubstituted at the site where the methyl is replacing the hydrogen) enhance the pharmacological efficacy of compounds, one of ordinary skill in the art, would be motivated to modify the prior art compound, to substitute methyl at the 2

position of the pyridine ring in place of the hydrogen. There are a limited number of places for this substitution to occur on the compound.

The applicant also traverses that the 103 (a) rejection was made in view of Blake, alleging that Blake teaches away from the applicant's isotopes. However, Blake does teach that generally stable isotopes are proving useful as tracers for drug distribution and metabolism studies. See page 385 of Blake et. al. Blake also teaches that the many advantages of stable isotopes for these purposes include the absence of possible radiation hazards, especially important where children and pregnant women are concerned. Here, the applicant's compounds are also used as labeling brain and peripheral nervous system structures involving mGlu5 receptors.

The instant compounds are radiolabeled bioisosteres of the prior art compounds.

It would have been obvious to one of ordinary skill in the art to synthesize radiolabeled bioisosteres of this class of compounds for use as neuroimagers since radiolabeled compounds radiolabeled with stable isotopes are useful as tracers for drug distribution and metabolism studies.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0670.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

/Binta M Robinson/
Examiner, Art Unit 1625

/Janet L. Andres/
Supervisory Patent Examiner, Art Unit 1625